

VI. CONCLUDING COMMENTS

Tobacco has been used in the Americas for three thousand years and its use has spread to nearly every culture in the world in the last five hundred years. Cigarette smokers puff a rod of burning tobacco and the majority of them inhale the smoke. As a consequence of smoke intake, a number of smoke constituents are absorbed and nicotine is the most active pharmacological ingredient of these compounds. Nicotine is absorbed very efficiently, enters the brain very quickly and a smoking dose is metabolised in 40 minutes which allows for brief duration of action. Smokers are sensitive to their plasma nicotine levels and they can control their intake of nicotine because of the rapidity of uptake and their perception of the moment to moment changes of nicotine level in their brain. Not only do smokers control nicotine by varying their cigarette consumption, but they control the strength of puffing to modify smoke generation, the amount of smoke retained for inhaling, and the degree of smoke inhalation for nicotine absorption. This control is more than avoidance of high toxic doses of nicotine but is an attempt to titrate for a specific nicotine dose by smoking high nicotine products less intensely and smoking low nicotine cigarettes more intensely.

The smoker's aim in titrating is obtaining an optimal dose of nicotine which will act on the body and satisfy some need. Experiments have revealed that nicotine has many actions on the body but only a very small proportion of these studies have used nicotine doses which are equivalent to smoking doses. The most consistent effect with smoking doses of nicotine is stimulation of a subset of the cholinergic neurones (ie the "nicotinic" pathways), including the autonomic nervous system and the ascending cholinergic pathways to the cortex and limbic system. The reason for this specificity of action is the similarity of the nicotine and acetylcholine molecules.

The outcome of these actions is an increase in blood levels of catecholamines and glucocorticoids and greater amounts of cortical desynchronization. All these changes are within the normal limits of the average person. Smokers believe that cigarettes alleviate mental and muscular fatigue to some extent and these effects can be attributed,

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in part, to the mobilization of energy reserves by the catecholamines and glucocorticoids. Smokers also claim that smoking helps them think and concentrate. Experimental studies with smokers have supported this claim and shown that nicotine can produce absolute enhancements in performance as well as preventing the performance decrements usually found during sustained performance. Enhanced performance of the same magnitude was found when nicotine tablets were given to non-smokers. A third important effect of nicotine is its sedative action which has been supported by questionnaire and experimental studies of smoking.

Measures of smoking behaviour during performance and while subjects are under stress show that smokers vary their nicotine intake according to the situation. In this way they obtain the required nicotine dose for stimulation or sedation depending on the situation. The rapid absorption and rapid metabolism make this substance suitable for hour-by-hour self-medication because of the personal control that can be exercised. In this respect nicotine is superior to other compounds for medication.

Nicotine taken in smoking doses seems to be relatively safe for healthy adults to use. On the evidence available at the moment it acts specifically on only a subset of the acetylcholine pathways in the body producing few side effects and none of these interfere with the normal functioning of body and mind. Even after a lifetime of use, the chronic toxicity of nicotine appears to be low. Thus nicotine stands in marked contrast to the deleterious short term and long term consequences of the socially acceptable substance, ethyl alcohol.

A number of important implications follow from these facts about nicotine. If smokers derive beneficial effects from nicotine and cigarettes are the most effective method of administering nicotine then cigarettes should be designed to deliver nicotine with minimum risk from smoke-related diseases. In my view the current trend of continuing to reduce nicotine as well as tar and carbon monoxide is not having the expected health benefits because smokers are compensating by puffing harder and inhaling more smoke. It has been argued that because compensation can only be partial with low delivery brands, intake of tar and carbon monoxide is still less than when high delivery brands were smoked and so

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these products have less risk (Rawbone, 1979). This argument would be true if cigarette consumption did not increase. However a recent paper (Wald et al, 1981) reported that over the 25 year period 1949-1974 sales-weighted average nicotine monotonically decreased. Tobacco industry figures confirm that sales-weighted nicotine monotonically decreased until 1975 from 1965, when its data were first available (RSL, 1981). In 1949, sales-weighted average nicotine was 74% higher than in 1974, representing a nicotine difference of 3.0% per annum. Over these 25 years, cigarette consumption for male smokers (RSL, 1981) increased by 50%, an average annual change of 2.0%, reflecting two-thirds compensation by consumption alone. The increase in consumption for women was even greater, as social influences contributed - it became more fashionable for females to smoke over this period. Since the mid-'70s, consumption has been affected by economic factors such as the recession and stringent tobacco taxation which make strong conclusions difficult. Nevertheless, it is intriguing that the recent downturn in consumption has coincided with a slight increase in average nicotine yield (Wald et al, 1981).

In conventional cigarette design, tar and nicotine tend to co-vary, ie low tar also entails low nicotine. Most popular cigarettes have a nicotine yield, as measured by a smoking machine, of at least 1.3 mg per cigarette, the best-selling brand having a nicotine yield of 1.6 mg per cigarette (DESS, 1981). Low tar cigarettes, however, have an average nicotine yield of only 0.7 mg per cigarette (about half popular requirement). Perhaps it is no coincidence that these low tar - low nicotine cigarettes have now, for a number of years, hovered around 15% market share - which is the same as the estimated proportion of "social smokers" (McKennell and Thomas, 1967), ie that minority group who, according to motivational researchers, smoke cigarettes for non-nicotine reasons (McKennell, 1973). For the majority of smokers, however, such low strength cigarettes are not satisfying: compensatory mechanisms became inadequate, as the effort necessary to generate required levels of nicotine is too great. A more effective approach for minimising risk and maximising benefit would be a product with medium nicotine delivery but a reduction of most other smoke components. For this concept to be acceptable, it is obviously crucial that such a cigarette also conveys sufficient flavour appeal. The Independent Scientific Committee already recognises the importance of flavour as a prerequisite for smoker satisfaction (Second Report, 1978). It is therefore essential that the product would not need to be smoked

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more intensively, or require more smoke to be inhaled, in order to satisfy taste, or to deliver the optimal amount of nicotine to the smoker. However, optimal levels of nicotine are different for different sorts of smokers. It seems to depend on such determinants as personality, sex, and average daily consumption. Thus specific types of products could be required to deliver the optimal nicotine levels for differing smoker groups.

The tobacco industry has methods for modifying smoke delivery in order to partially dissociate nicotine from tar. Some of the more drastic smoke reduction procedures change the chemical nature of the smoke (Guerin, 1980) and the toxicological implication of these shifts is unknown. Russell (1979) has briefly reported some tests of reduced tar, medium nicotine cigarettes but his comments imply that they were less acceptable than conventional products. Thus the manipulations of smoke delivery, that have been attempted so far, are very unsatisfactory, not only because they may leave harmful smoke compounds but because they remove important flavours. Clearly, future progress must be in the direction of reduction of specific smoke constituents to reduce risk but maintain flavour.

Unfortunately, we have only a limited amount of toxicological information on a few of the 4000 identified compounds in tobacco and tobacco smoke on which to base a selective reduction strategy. It is said that tobacco smoke is a relatively mild carcinogen (Tso, 1980) which means either that the hazardous compound or compounds are only weak carcinogens or the toxic compound is present in very small quantities. In the latter case the task of identification of the constituents to be reduced will be formidable.

Problems may also arise with the identification of key flavours because taste sensitivity is not uniform across the flavour spectrum. This non-uniformity means that some smoke constituents which are present in large amounts may contribute very little to smoke flavour while a trace component may be essential for a balanced sensory impact. Conceivably chemicals that are essential flavour components could also be hazardous (Second Report, 1978). In this case, non-toxic, flavour additives will have to be substituted for the desired flavour and to

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fortify the other flavours in order to preserve the characteristic full flavour impact for the smoker.

It is clear that the way to a less hazardous cigarette is not an easy one. However, the development of a medium nicotine cigarette, possibly with reduction of some smoke components, suitably enhanced with flavour, could well represent an important milestone along this path.

The end of the road could not only be a safer cigarette but also a more satisfying one. Nicotine has much to commend it.

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REFERENCES

ADAMS P I : Changes in personal smoking habits brought about by changes in cigarette smoke yield.

Proc 6th Int Tobacco Sci Cong, Tokyo: 102-108, 1976.

ADAMS P I : The influence of cigarette smoke yields on smoking habits.

In Smoking Behaviour, ed by R E Thornton, pp 349-360,
Churchill-Livingstone, Edinburgh, 1978.

ANDERSSON K : Effects of cigarette smoking on learning and retention.

Psychopharmacologia 41: 1-5, 1975a.

ANDERSSON K : Cigarette smoking, arousal and performance in a complex memory task.

Rep Dept Psychol Univer Stockholm, No.454, 1975b.

ANDERSSON K & HOCKEY, G R J : Effects of cigarette smoking on incidental memory.

Psychopharmacologia 52: 223-226, 1977.

ANDERSSON K & POST B : Effects of cigarette smoking on verbal rote learning and physiological arousal

Scand J Psychol 15: 263-267, 1974.

ARMITAGE A K : Some recent observations relating to the absorption of nicotine from tobacco smoke.

In Smoking Behaviour, ed by W L Dunn, pp 83-91, Winston (J Wiley), Washington DC, 1973.

ARMITAGE A K, DOLLERY C T, GEORGE C F, HOUSEMAN T H,

LEWIS P J and TURNER D M : Absorption and metabolism of nicotine by man during cigarette smoking.

Brit J Clin Pharmacol 1 : 180P-181P, 1974.

ARMITAGE A K, HALL G H and MORRISON C F : Pharmacological basis for the tobacco smoking habit.

Nature 217: 331-334, 1968.

1002973509

ARMITAGE A K, HALL G H and SELLERS C M : Effects of nicotine on
electrocortical activity and acetylcholine release from the cat
cerebral cortex.

Brit J Pharmacol 35: 152-150, 1969.

ARMITAGE A K and TURNER D M : Absorption of nicotine in cigarette and
cigar smoke through the oral mucosa
Nature 226: 1231-1232, 1970.

ARTHUR A J and GROB K : Nicotinabsorption aus dem Cigarettenrauch.
Z Präventivmed 9 : 14-25, 1964.

ASHTON H, MARSH V R, MILLMAN J E, RAWLINS M D, TELFORD R,
THOMPSON J W : The use of event-related slow potentials of the
brain as a means to analyse the effects of cigarette smoking and
nicotine in humans.
In Smoking Behaviour, ed by R E Thornton, pp 54-62,
Churchill-Livingstone, Edinburgh, 1978.

ASHTON H, MILLMAN J E, TELFORD R and THOMPSON J W : Stimulant and
depressant effects of cigarettes smoking on brain activity in man.
British Journal of Pharmacology 48: 715-717, 1973.

ASHTON H, MILLMAN J E, TELFORD R and THOMPSON J W : The effect of
caffeine, nitrazepam and cigarette smoking on the contingent
negative variation in man.
EEG Clin Neurophysiol 37: 59-71, 1974.

ASHTON H, MILLMAN J E, TELFORD R and THOMPSON J W : A comparison of
some physiological and psychological effects of propanolol and
diazepam in normal subjects.
British Journal of Clinical Pharmacology 3: 551-559, 1976.

ASHTON H, STEPNEY R, and THOMPSON J W : Smoking behaviour and nicotine
intake in smokers presented with a 'two-thirds' cigarette.
In Smoking Behaviour ed by R E Thornton, pp 315-329,
Churchill-Livingstone, Edinburgh, 1978.

1002973510

ASHTON H, STEPNEY R and THOMPSON J W : Self titration by cigarette holders.
 Brit Med J 2 : 357-360, 1979.

ASHTON H and TELFORD R : Blood carboxyhaemoglobin levels in smokers.
 Brit Med J 4 : 740, 1973.

ASHTON H and WATSON D W : Puffing frequency and nicotine intake in cigarette smokers.
 Brit Med J 3 : 679-681, 1970.

ASTRAND P O and RODAHL K : Textbook of Work Physiology
 McGraw-Hill, New York, 1970.

BALTER M B : Drug abuse: a conceptual analysis and overview of the current situation.

In Drug Use, ed by E Josephson and E E Carroll; pp 3-22,
 Hemisphere Press (J Wiley), Washington DC, 1974.

BECKETT A H : Effects of drug-drug and drug-food interactions on drug levels and performance in man.

In Chemical Influences on Behaviour, ed by R Porter and J Birch,
 pp 89-108, Churchill, Edinburgh, 1970.

BECKETT A H and TRIGGS E J : Buccal absorption of basic drugs and its application as an in vivo model of passive drug transfer through lipid membranes.

J Pharm Pharmacol 19 : Suppl: 315-415, 1967.

BINNIE C D and COMER A K : The effect of cigarette smoking on the contingent negative variation (CNV) and eye movement.

In Smoking Behaviour, ed by R E Thornton, pp 69-75,
 Churchill-Livingstone, Edinburgh, 1978.

BREIMER D D : Clinical pharmacokinetic and biopharmaceutical aspects of hypnotic drug therapy.

In Sleep Research, ed by R G Priest, A Pletscher and J Ward,
 pp 63-81, M.T.P. Press, Lancaster, UK, 1979.

1002973511

BRODIE B B, MAICKEL R P and JONDORF W R : Termination of drug action by enzymatic inactivation.

Fed Proc 17: 1163-1174, 1958.

CALIFANO J A : Remarks to the Fourth World Congress on Smoking and Health. In The Smoking Epidemic, ed by L M Ramstrom, pp 118-122, Almqvist and Wiksell, Stockholm, 1980.

CARRUTHERS M : Worrying about anxiety.

Scot Med J 20: 289-290, 1975.

CASTEDEN C M and COLE P V : Inhalation of tobacco smoke by pipe and cigar smokers.

Lancet 2 (7819): 21-22, 1973.

CELESIA G G and JASPER H H : Acetylcholine released from the cerebral cortex in relation to state of activation.

Neurology 16: 1053-1063, 1966.

CHERRY N and KIERNAN K : Personality scores and smoking behaviour - a longitudinal study.

Brit J Prevent Med 30: 123-131, 1976.

CHERRY N and KIERNAN K : A longitudinal study of smoking and personality. In Smoking Behaviour, ed by R E Thornton, pp 12-18, Churchill-Livingstone, Edinburgh, 1978.

CHRISTENSEN E H and HANSEN O : Arbeitsfahigkeit und ehrnahung. Skand Arch Physiol 81: 160-178, 1939.

COHEN A J and ROE F J C : Monograph on the Pharmacology and Toxicology of Nicotine. Tobacco Advisory Council, London, 1981.

COMER A K, BINNIE C D, BURNETT L, DARBY C E and THORNTON R E : The effect of cigarette smoking on the contingent negative variation (CNV) and eye movement.

(Abstract) EEG Clin Neurophysiol 39: 222, 1975.

1002973512

CREIGHTON D E and LEWIS P H : The effect of smoking pattern on smoke deliveries.

In Smoking Behaviour, ed by R E Thornton, pp 301-314,
Churchill-Livingstone, Edinburgh, 1978a.

CREIGHTON D E and LEWIS P H : The effect of different cigarettes on human smoking patterns.

In Smoking Behaviour, ed by R E Thornton, pp 289-300,
Churchill-Livingstone, Edinburgh, 1978b.

CRYER P E : Physiology and pathophysiology of the human sympathoadrenal neuroendocrine system.

New Engl J Med 303: 435-444, 1980.

CRYER P E, HAMMOND M W, SANTIAGO J V, and SHAH S D : Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events.

New Engl J Med 295: 573-577, 1976.

CURTIS D R and RYALL R W : The excitation of Renshaw cells by cholinomimetics.

Exp Brain Res 2: 49-55, 1966.

DALE H H : The action of certain esters and ethers of choline, and their relation to muscarine.

J Pharm Exp Therap 6: 147-190, 1914.

DHSS (Department of Health and Social Security)

Tar and Nicotine Table , 1981.

DOLL R and HILL A B : Mortality in relation to smoking: Ten years' observations of British doctors.

Brit Med J 1: 1399-1410 and 1460-1467, 1964.

DOMINO E F : Electroencephalographic and behavioural arousal effects of small doses of nicotine. A neuropsychopharmacological study.
Ann NY Acad Sci 142, 216-244, 1967.

1002973513

DONINO E F : Neuropsychopharmacology of nicotine and tobacco smoking.

In Smoking Behaviour: Motives and Incentives by W L Dunn

pp 5-31, Winston, (J Wiley), Washington DC, 1973.

DURNELL K and CARTWRIGHT A : Medicine Takers, Prescribers and Hoarders.

Routledge & Kegan Paul, London, 1972.

ECCLES J C, ECCLES R M, and FATT P : Pharmacological investigations on
a central synapse operated by acetylcholine.

J Physiol (Lond) 131: 154-169, 1956.

ECCLES J C and LIBET B: Origin and blockade of the synaptic
responses of curarized sympathetic ganglia.

J Physiol (Lond) 157: 484-503, 1956.

EDWARDS J : The psychophysiology of tobacco smoking.

In Electrocortical activity. Submitted for publication.

EDWARDS J, WESNES K, WARBURTON D M and GALE A : Event-Related
potentials and smoking. In preparation.

ENEROTH P, FUXE K, GUSTAFSSON J-Å, HÖKFELT T, LOFSTROM A,

SKETT P and AGNATI L : The effect of nicotine on central catecholamine
neurones and gonadotrophin secretion II.

Med Biol 55: 153-156, 1977a.

ENEROTH P, FUXE K, GUSTAFSSON J-Å, HÖKFELT T, LOFSTROM A,

SKETT P and AGNATI L : The effect of nicotine on central catecholamine
neurones and gonadotrophin secretion III.

Med Biol 55: 167-176, 1977b.

ESSMAN W B : Metabolic and behavioral consequences of nicotine.

In Drugs and Cerebral Function, ed by W L Smith, pp 46-84,
Charles C Thomas, Springfield US, 1981.

EVSENCK H J : Personality and cigarette smoking.

Life Sci 3: 777-792, 1963.

1002973514

99.

EYSENCK H J and EYSENCK S B G : Manual of the Eysenck Personality Inventory.
University of London Press, London, 1964.

FINNEGAN J K, LARSON P S and HAAG H B : The role of nicotine in the
cigarette habit.

Science 102: 94-96, 1945.

FISHER V E : An experimental study of the effects of tobacco smoking on
certain psychophysiological functions.

Comp Psychol Monog 4 No.19 whole issue, 1927.

FORBES W F, ROBINSON J C, HANLEY J A and COLBURN H N : Studies of the nicotine
exposure of individuals: I Changes in mouth level exposure to nicotine on
switching to lower nicotine cigarettes.
Int J Addic 11: 933-950, 1976.

FRANKENHAUSER M, MYRSTEN A L, POST B and JOHANSSON G : Behavioural
and physiological effects of cigarette smoking in a monotonous
situation.
Psychopharmacologia 22: 1-7, 1981.

FREEDMAN S, and FLETCHER C M : Changes of smoking habits and cough
in men smoking cigarettes with 30% NSM tobacco substitute.
Brit Med J 3: 1427-1430, 1976.

FRITH C D : Smoking behaviour and its relation to the smoker's
immediate experience.
Brit J Soc Clin Psychol 10: 73-78, 1981.

FURCHGOTT R F : Receptor mechanisms.
Ann Rev Pharmacol 4: 21-50, 1964.

FUXE K, AGNATI L, ENEROOTH P, GUSTAFSSON J-Å, HOKFELT J,
LOFSTROM A, SKETT B, and SKETT P : The effect of nicotine on
central catecholamine neurones and gonadotropin secretion I.
Med Biol 55: 148-157, 1977.

GILBERT R M : Caffeine as a drug of abuse.
In Research Advances in Alcohol and Drug Problems, Vol ed by
R J Gibbins, Y Israel, H Kalant, R E Popham, W Schmidt, R G Smart,
pp 49-176, Wiley, New York. 1976

1002923515

GOLDFARB T L and JARVIK J E : Accommodation to restricted tobacco smoke intake in cigarette smokers.

Int J Addict 7: 559-565, 1972.

GOLDFARB T L, JARVIK M E and GLICK S D : Cigarette nicotine content as a determinant of human smoking behaviour.

Psychopharmacologia 17: 89-93, 1980.

GRITZ E R, BAER-WEISS V and JARVIK M E : Titration of nicotine intake with full-length and half-length cigarettes.

Clin Pharmacol Therap 20: 552-556.

GUERIN, M R : Chemical composition of cigarette smoke.

In A Safe Cigarette? (Banbury Report 3), ed by G B Gori and F G Bock, pp 191-201, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1980.

GUILFORD J S : Factors Related to Successful Abstinence from Smoking.

Pittsburgh, American Institutes for Research, 1966.

GUILLERM R, MASUREL G, BROUSSELLE B, HYACINTHE R, SIMON A and HEE J : Effets cliniques et fonctionnels respiratoires de la substitution d'une cigarette peu irritante à la cigarette habituelle dans une groupe de grands fumeurs.

Les bronches 24: 209-231, 1974.

HALPERIN M E, McFARLAND R A, NIVEN J J and ROUGHTON F J W: The time course of the effects of carbon monoxide on visual thresholds.

J Physiol (Lond) 146: 583-593.

HEMMOND E C : Smoking in relation to the death rates of one million men and women.

In Epidemiological approaches to the Study of Cancer, ed by W Haenszel, pp 127-204, National Cancer Institute Monograph, US Department of Health, Education and Welfare, Washington DC, 1966.

HARRIS L S : Cannabis: A review of progress.

In Psychopharmacology: A Generation of Progress, ed by M A Lipton, A DiNascio, and K F Killam, pp 1565-1574, Raven Press, New York, 1978.

HAUSER E, SCHWARTZ B, ROTH G and BICKFORD R : Electroencephalographic changes related to smoking.

EEG Clin Neurophysiol

1002973516

Int J Addict 7: 559-565, 1972.

GOLDFARB T L, JARVIK M E and GLICK S D : Cigarette nicotine content as a determinant of human smoking behaviour.
Psychopharmacologia 17: 89-93, 1980.

GRITZ E R, BAER-WEISS V and JARVIK M E : Titration of nicotine intake with full-length and half-length cigarettes.
Clin Pharmacol Therap 20: 552-556.

GUERIN, M R : Chemical composition of cigarette smoke.

In A Safe Cigarette?(Banbury Report 3), ed by G B Gori and F G Bock, pp 191-201, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1980.

GUILFORD J S : Factors Related to Successful Abstinence from Smoking.
Pittsburgh, American Institutes for Research, 1966.

GUILLERM R, MASUREL G, BROUSSALLE B, HYACINTHE R, SIMON A and HEE J : Effets cliniques et fonctionnels respiratoires de la substitution d'une cigarette peu irritante à la cigarette habituelle dans une groupe de grands fumeurs.
Les bronches 24: 209-231, 1974.

HALPERIN M H, MCFARLAND R A, NIVEN J J and ROUGHTON F J W: The time course of the effects of carbon monoxide on visual thresholds.
J Physiol (Lond) 146: 583-593.

HAMMOND E C : Smoking in relation to the death rates of one million men and women.
In Epidemiological approaches to the Study of Cancer, ed by W Haenszel, pp 127-204, National Cancer Institute Monograph, US Department of Health, Education and Welfare, Washington DC, 1966.

HARRIS L S : Cannabis: A review of progress.

In Psychopharmacology: A Generation of Progress, ed by M A Lipton, A DiMascio, and K F Killam, pp 1565-1574, Raven Press, New York, 1978.

HAUSER H, SCHWARTZ B, ROTH G and BICKFORD R : Electroencephalographic changes related to smoking.
EEG. Clin. Neurophysiol., 10: 576
(Abstract), 1958.

1002923517

HEIMSTRA N W, BANCROFT N R and DeKOCK A R: Effects of smoking upon sustained performance in a simulated driving task.

Ann NY Acad Sci 142: 295-307, 1967.

HOUSTON J P, SCHNEIDER N G & JARVIK M E : Effects of smoking on free-recall and organization in short and long-term memory.

Am J Psychiatry 135: 220-222, 1978.

BOUTAKKER R S and TAYLOR L D : Consumer Demand in the United States, 1929 - 1970. Harvard University Press, Cambridge, Mass, 1966.

ERDINA P D : Metabolism of brain acetylcholine and its modification by drugs.

Drug Metab. Rev 3: 89-129, 1974.

HULL C : The influence of tobacco smoking on mental and motor efficiency. Psychol Monog 33: No.150, 1924.

HUNT W A, BESPALEC D A : An evaluation of current methods of modifying smoking behaviour. J Clin Psychol 30: 431-438, 1974.

ISRAEL Y and MARDONES J : Biological Basis of Alcoholism Wiley, New York, 1971.

JARVIK M E, GLICK S D, NAKAMURA R K : Inhibition of cigarette smoking by orally administered nicotine.

Clin Pharmacol Therap 11: 574-576, 1980.

JARVIK M E, POPEK P, SCHNEIDER N G, BAER-WEISS V and GRITZ E R : Can cigarette size and nicotine content influence smoking and puffing rates.

Psychopharmacology 58: 303-306, 1978.

KATZ B and THESLEFF S : A study of desensitization produced by acetylcholine at the motor end plate.

J Physiol, London 138: 63-80, 1957.

1002923518

NAKANURA H and DOMINO E F : Differential actions of α and β cholinergic agonists on the brainstem activating system.

Int J Neuropharm 8: 105-115, 1969.

KERSHBAUM A and BELLET S : Cigarette, cigar and pipe smoking: Some differences in biochemical effects.

Geriatrics 23: 126-134, 1968.

KERSHBAUM A, PAPPAJOHN D J, BELLET S, HIRABAYASHI M and SEAFIIHA H: Effect of smoking and nicotine on adrenocortical secretion.

J Amer Med Assoc 203: 275-278, 1968.

FILCH L G and BRANDON S : Habituation and addiction to amphetamines.

Brit Med J 2: 40-43, 1962.

KISSIN B : Alcohol as it compares to other addictive substances.

In Drug Abuse, ed by W Keup, pp 251-262

Charles C Thomas, Springfield, Ill, 1972.

KRAPP D E and DOMINO E F : Action of nicotine on the ascending reticular activating system.

Int J Neuropharm 1: 333-351, 1962.

KNOTT V J : Psychophysiological correlates of smokers and non-smokers: studies on cortical, autonomic and behavioural responsivity.

In Electrophysiological Effects of Nicotine, ed by A Remond and C Izard, pp 99-116, Elsevier - North Holland Biomedical Press, Amsterdam, 1979.

KORNETSKY C : Pharmacology: Drugs Affecting Behavior.

Wiley, New York, 1976.

KUMAR R, COOKE E C, LADER M E, and RUSSELL M A H : Is nicotine important in tobacco smoking?

Clin Pharm Therap 21: 520-529, 1977.

1002973519

LARSSON P S, FINNEGAR J, and HAAG H B : Observations on the effect of cigarette smoking on the fusion frequency of flicker.
J Clin Invest 29: 483-486, 1950.

LARSSON P S, HAAG H B and SILVETTE H : Tobacco: Experimental and Clinical Studies, Williams & Wilkins Co, Baltimore, 1961.

LATIES V G and MERIGAN W H : Behavioural effects of carbon monoxide on animals and man.
Ann Rev Pharmacol Toxicol 19: 357-392, 1979.

LEE P N : Has the mortality of male doctors improved with the reductions in their cigarette smoking?
Brit Med J 2: 1538-1540, 1979.

LEMBERGER L and RUBIN A : Physiological Disposition of Drugs of Abuse. Spectrum (J Wiley), New York, 1976.

LICHENSTEIGER W : Interaction of acetylcholine in neuroendocrine function. In Biologique Cellulaire des Processus Neurosecrétatoires Hypothalamiques, ed by J C Vincent and C Kornon, pp 179-191, Collèques Internationaux du C.N.R.S., Paris, 1979.

LICHENSTEIGER W, FELIX D, LIENHART R and HEFTI F : A quantitative correlation between single unit activity and fluorescence intensity of dopamine neurones in zona compacta of substantia nigra, as demonstrated under the influence of nicotine and physostigmine.
Brain Res 117: 85-103, 1976.

LICHENSTEIGER W, RICHARDS J G and KOPP H G : Changes in the distribution of non-neuronal units in rat median eminence and in anterior pituitary hormone secretion after activation of tuberoinfundibular dopamine neurones by brain stimulation or nicotine.
Brain Res 157: 13-88, 1978.

LUCCHESI B R, SCHUSTER C R, and EMLEY G S : The role of nicotine as a determinant of cigarette smoking frequency in man with observations of certain cardiovascular effects associated with the tobacco alkaloid.

Clin Pharm Therap 8: 789-796, 1967.

1002923520

MacMAHON B, YEN S, TRICHOPOULOS D, WARREN K and NARDI G : Coffee and
Cancer of the Pancreas

New Eng J Med 304: 630-633, 1981.

MARKS J : The Benzodiazepines: Use, Overuse, Misuse, Abuse.

M.T.P. Press, Lancaster, UK, 1978.

MARKS V and KELLY J F : Absorption of caffeine from tea, coffee and
Coca Cola.

Lancet 1: 827, 1973.

MARLATT A : A cognitive-behavioral model of the relapse process.

In Behavioural Analysis and Treatment of Substance Abuse, ed by
J Krasnegor, pp 191-199, National Institute for Drug Abuse,
Washington, DC, 1979.

MAUSNER J S : Cigarette smoking among patients with respiratory disease.

Ann Rev Respir Dis 102: 704-706.

McKENNELL A C : Smoking motivation factors.

Brit J Soc Clin Psychol 9: 8-22, 1970.

McKENNELL A C : A Comparison of Two Smoking Typologies

TRC Research Paper 12, 1973.

McKENNELL A C and THOMAS R K : Adults and Adolescents' Smoking Habits
and Attitudes.

EMSO, 1967.

MEARES R, GRIMWADE J, BICKLEY M, and WOOD C : Smoking and neuroticism.

Lancet 2 : 770, 1971.

MURPHREE, E B : EEG effects in humans of nicotine, tobacco smoking,
withdrawal from smoking and possible surrogates.

In Electrophysiological Effects of Nicotine, ed by A Rémond and
C Ezard, pp 227-244, Elsevier - North Holland Biomedical Press,
Amsterdam, 1979.

1002973521

MYRSTEN A-L, ANDERSSON K, FRANKENHAEUSER M and NARDH A : Immediate effects of cigarette smoking as related to different smoking habits.
Rep Psychol Labs 378, Univ Stockholm, Stockholm, 1972.

MYRSTEN A-L, POST B, FRANKENHAEUSER M, JOHANSSON G : Changes in behavioural and physiological activation induced by cigarette smoking in habitual smokers. Psychopharmacologia 27: 305-312, 1972.

NESBITT P D : Smoking, physiological arousal and emotional response. Journal of Personality and Social Psychology 25: 137-144, 1973.

OLDENDORF W B : Distribution of drugs in the brain.

In Psychopharmacology in the Practice of Medicine, ed by M E Jarvik, pp 167-175, Appleton-Century-Crofts, New York, 1977.

OLDENDORF W B, HYMAN S, BRAUN L, OLDENDORF S Z: Blood-brain barrier: penetration of morphine, codeine, heroine and methadone after carotid injection.
Science, 176: 984-987, 1972.

OVIEDO Y VALDES G F DE: Historia general y natural de las Indias.
Quoted in Robicack, 1978.

PANGBORN R M and TRABUE I M : Gustatory responses during periods of controlled and ad lib cigarette smoking.
Percep Psychophys 1 : 139-144, 1973.

PATON W D M and PERRY W L M : The relationship between depolarization and block in the cat's superior cervical ganglion.
J Physiol (London) 119: 43-57, 1953.

PAULING P : The conformation of molecules affecting cholinergic nervous systems. In Drugs and Cholinergic Mechanisms in the CNS, ed by E Heilbronn and A Winter, Research Institute of National Defence, Stockholm, 1980.

PEPEU G : Nicotina e acetilcolina cerebrale.
Arch Ital Sci Farmacol, 15: 93-94, 1965.

1002973522

PROOSDIJ C : Smoking, its influence on the individual and its role in social medicine.
Elsevier, New York, 1960.

RAE G : Extraversion, neuroticism and cigarette smoking.
Brit J Soc Clin Psychol 14: 429-430, 1975.

RAWBONE R G : Nicotine, tobacco substitutes and smoking habits.
Brit Med J 2: 177, 1976.

RAWBONE R G : Self-titration by cigarette smokers.
Brit Med J 2: 731-732, 1979.

RAWBONE R G, MURPHY K, TATE M E and KANE S J : The analysis of smoking parameters, inhalation and absorption of tobacco smoke in studies of human smoking behaviour.
In Smoking Behaviour, ed by R E Thornton, pp 171-194, Churchill-Livingstone, Edinburgh, 1978.

ROYAL COLLEGE OF PHYSICIANS: Smoking and Health
Pitman, London, 1962.

RSL (Research Services Limited): TAC Statistics of Smoking.
(J.2770/AS), 1981.

RUSSELL M A H : Tobacco smoking and nicotine dependence.
In Research Advances in Alcohol and Drug Problems, Vol 3,
ed by R J Gibbins, Y Israel, B Kalant, R E Popham, W Schmidt,
and R G Smart, pp 1-48, Wiley, New York, 1976.

RUSSELL M A H : Low tar - medium nicotine cigarettes: a new approach to safer smoking.
Brit Med J 1: 1430-1433, 1976.

RUSSELL M A H, JARVIS M J and FEYERABEND C: A new age for snuff?
Lancet 1: 474-475.

RUSSELL M A H : Prevention of smoke-related disease.
In Prospects for Prevention, ed A T Proudfoot,
pp 55-74, Royal College of Physicians, Edinburgh, 1979.

1002973523

RUSSELL M A H, SUTTON S R, FEYERABEND C and SALOOJEE Y : Smokers response to shortened cigarettes: Dose reduction without dilution of tobacco smoke.

Clin Pharmacol Therap 27: 210-218, 1980.

RUSSELL M A H, PETO J and PATEL U A : The classification of smoking by factorial structure of motives.

J Roy Stat Soc A 137: 313-333, 1974.

RUSSELL M A H, SUTTON S R, FEYERABEND C and COLE P V : Addiction Research Unit nicotine titration studies.

In Smoking Behaviour, ed R E Thornton, pp 336-348, Churchill-Livingstone, Edinburgh, 1978.

RUSSELL M A H and WESNES K

Unpublished data.

RUSSELL M A H, WILSON C, FEYERABEND C and COLE P V : Effect of nicotine chewing gum as substitute for smoking.

Brit Med J 2: 391-393.

RUSSELL M A H, WILSON C, PATEL U A, COLE P V and FEYERABEND C : Comparison of effect on tobacco consumption and carbon monoxide absorption of changing to high and low nicotine cigarettes.

Brit Med J 4: 512-516, 1973.

RUSSELL M A H, WILSON C, PATEL U A, FEYERABEND C and COLE P V : Plasma nicotine levels after smoking cigarettes with high, medium and low nicotine yields.

Brit Med J 2: 414-416, 1975.

SCHACHTER S : Nicotine regulation in heavy and light smokers.

J Exp Psychol 106: 5-12, 1977.

SCHACHTER S : Pharmacological and psychological determinants of smoking.
Ann Int Med 88: 104-114, 1978a.

1002973524

SCHACHTER S : Pharmacological and psychological determinants of smoking.

In Smoking Behaviour ed by R E Thornton, pp 208-228,
Churchill-Livingstone, Edinburgh, 1978b.

SCHACHTER S, KOZLOWSKI L, and SILVERSTEIN B : Effects of urinary pH
on cigarette smoking.

J Exp Psychol 106: 13-19, 1977.

SCHECHTER M D, and RAND M J : Effect of acute deprivation of smoking on
aggression and hostility.

Psychopharmacologia 35: 19-28, 1974.

SCHMITTERLOH C G, HANSSON E, ANDERSSON G, APPELGREN L E and HOFFMAN P C :
Distribution of nicotine in the central nervous system.
Ann NY Acad Sci, 142: 2-14, 1967.

SCHULTES T W : The future of plants as sources of new biodynamic
compounds.

In Plants in the Development of Modern Medicine, ed by T Swain,
pp 103-124, Harvard University Press, Cambridge, Mass, 1972.

SECOND REPORT OF THE INDEPENDENT SCIENTIFIC COMMITTEE ON SMOKING AND
HEALTH: Developments in Tobacco Products and the Possibility
of "Lower-Risk" Cigarettes.

HMSO (ISBN: 0-11-320717-4) p4, 1978.

SHIFFMAN S M : The tobacco withdrawal syndrome.

In Cigarette Smoking as a Dependence Process, ed by N A
National Institute for Drug Abuse, Washington DC, 1979a.

SHIFFMAN S M : Analysis of relapse episodes following smoking cessation.
Paper presented at the 4th World Congress on Smoking and Health.

SHIFFMAN S M and JARVIK M E : Smoking withdrawal symptoms in two weeks
of abstinence.

Psychopharmacology, 50: 35-39, 1976.

1002973525

SHUTE C C D and LEWIS P R : The ascending cholinergic reticular system: neocortical, olfactory and subcortical projections.
Brain, 90: 497-520, 1967.

STALEANDSKY T : Effects of increased liver metabolism of nicotine on its uptake, elimination and toxicity in mice.
Acta Physiol Scand 80: 222-234, 1970.

STOLERMAN I P, GOLDFARB T, FINK R, and JARVIC M E : Influencing cigarette smoking with nicotine antagonists.
Psychopharmacologia 28: 247-259, 1973.

SUTTON S R, RUSSELL M A H, FEYERABEND C and SALOOJEE Y : Smokers response to dilution of smoke by ventilated cigarette holders.
In Smoking Behaviour, ed by R E Thornton, pp 330-335,
Churchill-Livingstone, Edinburgh, 1978.

TARRIERE C and HARTEMANN F : Investigation into the effects of tobacco smoke on a visual vigilance task.
Ergonomics, Proc 2nd Int Eng Assoc Cong, 525, 530, 1964.

TEMPLE D J : The absorption of nicotine from tobacco snuff through the nasal mucosa.
Arch Pharm 509: 984-987, 1976.

THOMAS C B : The relationship of smoking and habits of nervous tension.
In Smoking Behaviour, ed W L Dunn, pp 157-170, Winston (J Wiley),
New York, 1973.

TODD G F : Statistics of Smoking in the United Kingdom (5th Edition).
Tobacco Research Council, London, 1969.

TODD G F : Statistics of Smoking in the United Kingdom (6th Edition).
Tobacco Research Council, London, 1972.

TRAVELL J : Absorption of nicotine from various sites.
Ann NY Acad Sci 90: 13-30, 1960.

1002923526

TSO T C : Modification through agricultural techniques for developing safer tobacco.

In A Safe Cigarette? (Banbury Report 3), ed by G B Gori and F G Bock, pp 181-189, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1980.

TURNER J A M, SILLETT R W and BALL K P : Some effects of changing to low-tar and low-nicotine cigarettes.

Lancet 2: 737-739, 1974.

US DEPARTMENT OF HEALTH AND HUMAN SERVICES: The Health Consequences of Smoking - Cancer.

Report of the Surgeon General, 1981.

US PUBLIC HEALTH SERVICE: The Health Consequences of Smoking.

A report to the Surgeon General: 1964 US Department of Health, Education and Welfare. Washington DC, 1964.

US PUBLIC HEALTH SERVICE : Smoking and Health.

A report to the Surgeon General: 1979. US Department of Health, Education, and Welfare, Washington DC, 1979.

WAINGROW S and HORN D : Relationship of number of cigarettes smoked to "tar" rating.

Nat Cancer Inst Mong 28: 29-33, 1968.

WALD N, DOLL R and COPELAND G : Trends in tar, nicotine and carbon monoxide yields of UK cigarettes manufacturered since 1934.

Brit Med J 282: 763-765, 1981.

WALLGREN H and BARRY H : Actions of Alcohol.

Elsevier, Amsterdam, 1971.

WARBURTON D M : Brain, Behaviour and Drugs.

Wiley, London, 1975.

WARBURTON D M : Stimulus selection and behavioural inhibition?

In Handbook of Psychopharmacology, Vol 8, ed L L Iversen, S D Iversen, and S H Snyder, pp 131-147, Plenum Press, New York, 1977.

1002973522

TSO T C : Modification through agricultural techniques for developing safer tobacco.

In A Safe Cigarette? (Banbury Report 3), ed by G B Gori and F G Bock, pp 161-189, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1980.

TURNER J A M, SILLETT R W and BALL K P : Some effects of changing to low-tar and low-nicotine cigarettes.

Lancet 2: 737-739, 1974.

US DEPARTMENT OF HEALTH AND HUMAN SERVICES: The Health Consequences of Smoking - Cancer.

Report of the Surgeon General, 1981.

US PUBLIC HEALTH SERVICE: The Health Consequences of Smoking.

A report to the Surgeon General: 1964 US Department of Health, Education and Welfare. Washington DC, 1964.

US PUBLIC HEALTH SERVICE : Smoking and Health.

A report to the Surgeon General: 1979. US Department of Health, Education, and Welfare, Washington DC, 1979.

WAINGROW S and HORN D : Relationship of number of cigarettes smoked to "tar" rating.

Nat Cancer Inst Monogr 28: 29-33, 1968.

WALD N, DOLL R and COPELAND G : Trends in tar, nicotine and carbon monoxide yields of UK cigarettes manufactured since 1934.

Brit Med J 282: 763-765, 1981.

WALLGREN E and BARRY H : Actions of Alcohol.

Elsevier, Amsterdam, 1971.

WARBURTON D M : Brain, Behaviour and Drugs.

Wiley, London, 1975.

WARBURTON D M : Stimulus selection and behavioural inhibition.

In Handbook of Psychopharmacology, Vol 8, ed L L Iversen, S D Iversen, and S H Snyder, pp 131-147, Plenum Press, New York, 1977.

1002973528

WARBURTON D M : Physiological aspect of anxiety and schizophrenia.
In Stress and Cognition, ed by V Hamilton and D M Warburton
pp 431-468, Wiley, London, 1979.

WARBURTON D M : Neurochemical bases of behaviour.
Brit Med Bull 37: 121-125, 1981.

WARBURTON D M and WESNES K : Individual differences in smoking
and attentional performance.
In Smoking Behaviour, ed by R E Thornton, pp 19-43,
Churchill-Livingstone, Edinburgh, 1978.

WARBURTON D M and WESNES K : The role of electrocortical arousal in
the smoking habit.
In Electrophysiological Effects of Nicotine, ed by A Remond and
C Izard, pp 183-200, Elsevier - North Holland Biomedical Press, 1979.

WARBURTON D M, WESNES K and REVELL A : Personality factors in self-
medication by smoking.
In Response Variability to Psychotropic Drugs, ed by W Janke,
in press, Pergamon Press, London, 1982.

WARBURTON D M, WESNES K and SHERGOLD K : Facilitation of learning
and state dependency with nicotine.
Proc 13th C.I.N.P. Cong, in press.

WARWICK K M and EYSENCK H J : The effects of smoking on the CFF
threshold.
Life Sci 4: 219-225, 1963.

WATERS W E : Smoking and neuroticism.
Brit J Prevent Soc Med 25: 162-164, 1971.

WESNES K, PITKETHLY G M and WARBURTON D M : Oral Nicotine preload
and smoking behaviour, in preparation.

WESNES K and WARBURTON D M : The effects of cigarettes smoking and
nicotine tablets upon human attention.
In Smoking Behaviour, ed R E Thornton, pp 131-147,
Churchill-Livingstone, Edinburgh, 1978.

1002973529

WESNES K and WARBURTON D M : Stress, drugs and performance, ed by G R J Hockey
In Stress and Fatigue in Human Performance, in press,
Wiley, London, 1983.

WESTFALL T C, FLEMING R M, FUDGER M F and CLARK W G : Effect of nicotine
and related substances upon amine levels in the brain.
Ann NY Acad Sci 142: 83-100, 1967.

WESTFALL T C : Effect of nicotine and other drugs on the release of
³H-norepinephrine and ³H-dopamine from rat brain slices.
Neuropharm 13: 693-800, 1974.

WINTERNITZ W W and QUILLEN D : Acute hormonal response to cigarette smoking.
J Clin Pharm 17: 389-397, 1977.

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